Emerging health issues from chronic pesticide exposure: Innovative methodologies and effects on molecular cell and tissue level

Pesticides differ from other chemical substances for at least three important reasons: firstly, since they are designed to interfere with biochemical and metabolic processes of various species they are necessarily characterized by some degree of toxicity; secondly since they need to reach their targets to be effective, they are necessarily spread to the environment where they constitute a source of potentially dangerous exposure for workers and the general population; and thirdly since their toxicity is not fully specific for their targets, they can simultaneously endanger other non-target species, including humans. Another key characteristic is that, despite their toxicity and the environmental and health risks they bring about, pesticides are a necessary component of modern agriculture. Indeed, it is estimated that without their use a proportion of up to more than 50% of crops could be lost, in particular in the warm climates typical of developing countries. Therefore, pesticide regulation has to balance the risks associated with pesticide use against the benefits of a sustainable food supply.

Acute pesticide toxicity is a property well known and described in dossiers prepared for the use authorization, in the existing reports of acute poisoning as well as from a large body of published epidemiological studies. Usually the acute effects observed in human are a consequence of the same mechanisms of toxicity responsible for pesticide agrochemical activity. Examples of these diverse mechanisms include acetylcholinesterase inhibition and cholinergic syndrome for organophosphorous compounds and carbamates, production of reactive oxygen species through a mechanism of action involving redox cycling for paraquat, effect on nervous system sodium channels for DDT, impairment of coagulation for coumarine derivatives, etc. Acute toxicity involving pesticides causes several thousand acute poisonings per year worldwide; the vast majority of serious and fatal poisonings is due to deliberate self-harm, particularly in developing countries, but also occupational and accidental poisonings are present; the global burden for these latter events is unknown, but very likely it is in the order of several thousand fatalities out of hundreds of thousands of poisonings.

On the other hand, there are considerable uncertainties concerning health risks as a consequence long term and low dose pesticide exposure. This is exemplified by the contrasting results of epidemiological studies which in some cases confirm and in other cases exclude the involvement of pesticides in the investigated effects. An important factor in these apparent discrepancies is the difficulty in reliable identification of exposed and control groups, specifically, as pointed out by most epidemiological studies, the problem of performing a sound retrospective exposure assessment. Furthermore, the characteristics of exposure, in particular concerning duration and involvement of complex and variable mixtures typical of agricultural use, make any epidemiological approach very difficult.

Thus, even in presence of convincing epidemiological associations, very often no sound conclusion about the causal relationship between the long term exposure and respective effect can be drawn. Apart from the difficulties in ascertaining reliable exposure estimates this is also due to the uncertainties and doubts regarding the mechanisms of toxicity which, in the case of chronic and long term outcomes, can be different from the commercially exploited mechanism of action. Therefore, it is clear that the capacity of a specific compound to cause a defined effect can be toxicologically proven only when the whole chain of events from the exposure to the respective effect is known and well defined. Apart from the difficulties of defining chronic exposure and disease outcomes, the existence of a series of confounders/factors/variables of interest like lifestyle, occupation, diet, and smoking in the epidemiological investigation of the disease-exposure relationship must also be taken into account.

Therefore, collecting sound information regarding mechanisms of pesticide action is an objective particularly timely and needed. Indeed, filling the existing gaps may help not only in improving scientific knowledge on this important issue but also in refining risk assessment strategies, supporting decision making processes in pesticide authorization and restriction, as well as in improving the capacity of occupational health physicians to make diagnosis of occupational diseases. Collecting and summarizing updated information on mechanisms of pesticide action is not only an academic exercise but an activity directed at improving the levels of safety related to the “necessary” use of pesticides worldwide.

For these compelling reasons we have accepted the very kind invitation of this Journal to be the editors of a special issue on pesticides. In conclusion, at the end of this effort, we can express our satisfaction with the results. More than 25 renowned, invited scientists have contributed to this effort, resulting in a total of 17 papers being submitted, peer reviewed, accepted for publication and constituting a part of this special issue which covers, in our opinion, the main scientific controversies existing on the subject.

In particular, the problem of the exposure to mixtures has been elegantly addressed by Hernandez Jerez and co-workers, who have pointed out that the possibility of different forms of interaction among the components of a mixture (reciprocal independence, dose addition, synergy or antagonism) should always be considered and importantly that the involvement of different mechanisms of
action of the mixture’s components should likewise be taken into account. Among these, the mechanistic aspects of oxidative stress (OS) are frequently hypothesized in epidemiological and laboratory studies. This key issue has been raised in the experimental mechanistic study of Subbiah and co-workers, who have shown that OS might be at the basis of a possible cardiotoxic effect exerted by monocrotalines, which is thus implicated as an environmental cardiovascular risk factor. Utilizing the same mechanisms of action, other pesticides diazinon and propoxur may affect liver and kidney (Tsatsakis and co-workers). OS may also modulate, in exposed workers, the intraerythrocyte levels of the enzymes delta-9-aminolevulinic acid dehydratase (ALAD) and superoxide dismutase (SOD). Furthermore, it seems that the susceptibility to such effects can be affected by different genetic risk factors, including polymorphisms of pesticide metabolizing enzymes such as paraoxonase-1 (PON1), glutathione-S-transferases (GST) and plasma cholinesterase variants (BChE) and their consequences on levels of erythrocyte antioxidant enzymes (SOD, catalase, glutathione peroxidase, glucose-6-phosphate dehydrogenase and ALA-D) (Hernandez Jerez and co-workers). Genetic polymorphisms, in particular of PON1, have been identified as a possible risk factor for haemolymphopoietic cancer risk by Hadjichristodoulou and co-workers, while the same polymorphism has been shown as a possible determinant of vulnerability to organophosphorus compounds’ (OPs) neurotoxic effects, including developmental toxicity (Costa and co-workers). The large body of evidence of pesticide induced immunotoxicity in humans has been reviewed in depth by Corsini and co-workers who have also collected data regarding the possible dose–effect relationship for this kind of effects. Moretto and Colosio have reviewed the existing evidence of relationship between pesticide exposure and Parkinson Disease (PD) risk, concluding that the existing epidemiological evidence provides little support for a causal correlation between pesticide exposure and PD development in humans, but that a possible role of acute poisonings or episodes of excessive exposure, and/or of combined exposures especially at early age and/or in the presence of certain genetic variants can be hypothesised. On the same topic, Hadjigeorgiou and co-workers have provided some evidence that genetic susceptibility, mitochondrial dysfunction, oxidative stress and neuronal loss may predispose individuals to PD upon pesticide exposure, whilst Zaganas et al. have addressed, in their review, the current evidence of a possible link between pesticide exposure and dementia.

In some cases, pesticides whose use has been discontinued for many decades continue to represent a public health threat due to their persistence and their ability to migrate through the atmosphere for thousands of kilometres away from the place of original application. Characteristic is the case of DDT and other organochlorinated pesticides, whose mechanisms of toxicity have been explored and presented by Mrema et al. and Androustopoulos et al. These authors have mainly addressed important MECHANISTIC issues, focusing not only on persistent pollutants (POPs) but also on OPs, in particular regarding potential non-cholinergic mechanisms after long-term and low-dose exposure.

Pesticide and cancer risk has been concisely addressed by Vakonaki et al., in their minireview regarding recent in vitro findings on pesticides oncogenic modulation, mediated through the activation or dysregulation of oncogenes and tumor suppressor genes. Bollati and co-workers, have explored the capacity of pesticides to act as epigenetic toxicants, defined as being able to modify gene expression without being endowed with any mutagenic capacity. The capacity of some pesticides to physically link biological macromolecules through the synthesis of protein adducts has been addressed in the paper prepared by Furlong and co-workers, who conclude that these adducts can be used as biomarkers of exposure to OPs.

The relationship between pesticides and fertility is a very timely and important topic, in light of the paper from Perry and co-workers providing updated and relevant information on human sperm parameters in pesticide exposed workers, by presenting the published studies showing associations between pesticides and semen quality. Endocrine disruption, addressed by Mrema et al. in their paper, has been further investigated by Hernandez Jerez and co-workers, who have pointed out that OP exposure may increase serum levels of follicle-stimulating hormone and prolactin while causing a decrease in serum testosterone and inhibit B levels, and that in some cases exposure is associated with a reduction of serum luteinizing hormone (LH). These authors therefore suggest that OPs may have an impact on the endocrine function.

We can conclude that in this special issue all the main current topics regarding pesticide mechanisms of actions have been addressed, many of the pending questions have found answers but have also highlighted many issues, worthwhile to be further explored by toxicological and epidemiological research.


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